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EXAMINER

HM11/1207

CATHRYN CAMPBELL
CAMPBELL AND FLORES
4370 LA JOLLA VILLAGE DRIVE
SUITE 700
SAN DIEGO CA 92122

ART UNIT	PAPER NUMBER
1646	18

DATE MAILED: 12/07/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 09/24/98 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-5, 7, 8, 16-33, 66-77 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-5, 7, 8, 16-33, 66-77 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

1) Claims 1 to 5, 7, 8, 16 to 33 and 66 to 77 are pending in the instant application. Claims 7, 8, 22, 26, 31, 32, and 77 have been amended and claims 6, 9 to 15 and 78 to 81 have been canceled as requested by Applicant in Paper Number 17, filed 24 September of 1998.

2) Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4) Claims 1, 3 to 5 and 80 stand rejected under 35 U.S.C. 101 as encompassing non-statutory subject matter. Applicant has traversed this rejection on the premise the term Fusion protein does not encompass T cell receptors from the immunoglobulin superfamily. If Applicant will kindly review the art of immunology on the mechanism by which genes encoding immunoglobulin chains are generated they will see that members of the immunoglobulin superfamily which contain variable heavy and variable light chains certainly qualify as fusion proteins.

5) Claims 7, 8 and 77 are rejected under 35 U.S.C. § 101 because they are drawn to a nonfunctional invention. These claims further limit claim 1 in requiring the plurality of cells to produce bacteriophage without limiting these cells to bacterial cells. If these claims were to depend from claim 2 this rejection would be avoided.

6) Claims 1 to 5, 7, 8, 16 to 33 and 68 to 75 stand provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1 to 33 and 68 to 75 of copending Application No. 08/470,297 for those reasons of record in section 8 of Paper Number 12.

7) Claims 1 to 5, 7, 8 and 16 to 33 stand provisionally rejected under the judicially

created doctrine of obviousness-type double patenting as being unpatentable over claims 1 to 8, 16 to 21 and 23 to 33 of copending Application No. 08/349,131 for those reasons of record in section 9 of Paper Number 12.

8) Claims 1 to 5, 7, 8, 16 to 33 and 66 to 77 stand rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling for those reasons of record as applied to claims 1 to 33 and 66 to 81 in section 10 of Paper Number 12. The instant claims encompass a plurality of cells each containing a first and second nucleic acid encoding a first and second polypeptide. The only method of producing such a cell that is described in the instant specification requires two vectors which each contain two pairs of restriction endonuclease cleavage sites symmetrically oriented around a cloning site and which vectors can be operably combined to form a single vector. As stated in the "SUMMARY OF THE INVENTION", the instant invention involves the production of a plurality of heteromeric receptors "on the surface of a cell" by generating a plurality of cells containing diverse combinations of first and second DNA sequences encoding first and second polypeptides which combine to form those receptors. The "DETAILED DESCRIPTION OF THE INVENTION" states that "[t]he method is advantageous in that only proper combinations of vector portions are randomly brought together for the coexpression of different DNA sequences without loss of population size or diversity". The instant claims do not currently reflect those elements which the specification expressly identifies as the inventive contribution of Applicant. The proper portion of each of the vectors of the claimed invention would be those portions encoding the polypeptides which combine to form the receptors. To be employed in the manner that is disclosed in the instant specification the protein coding portion of each vector employed in the production of

the claimed cell must only be able to join to the corresponding portion of the other vector when processed as described. However, simply incorporating a DNA encoding a protein between two pairs of symmetrically oriented restriction sites in a vector which is otherwise unrelated to a second vector containing a DNA encoding a protein wherein the second DNA is located between those same two restriction sites in opposite orientation will not facilitate the joining of only the coding portions of those two vectors into a single vector.

To illustrate this point, it is noted that the example in the instant specification employs the cleavage sites which are the substrates of the two restriction endonucleases MluI and HindIII. If one cleaves a first vector containing two symmetrically oriented pairs of MluI and HindIII recognition sites with the restriction endonuclease MluI, as shown in Figure I of the instant application, one will produce two linear molecules with four identical single stranded ends each having the sequence 5'-CGCG-3'. If one then produces a second vector which is otherwise unrelated to the first vector except for the presence of the same two pairs of symmetrically oriented cleavage sites and cleaves that vector with the restriction endonuclease HindIII they will also produce two linear molecules with four identical single stranded ends each having the sequence 5'-AGCT-3'. If one attempts to ligate these molecules to one another there is absolutely nothing to support a conclusion that only the linear molecule containing the uncleaved HindIII sites from the first vector will operably and selectively join to only the linear molecule containing the uncleaved MluI sites from the second vector. On the contrary, because the "sticky ends" from the two different vectors are not complementary one would reasonable expect the ends of each linear molecule to only ligate to an end of a linear molecule from the same vector. Therefore, the instant claims do not recite those material elements which reflect

Applicant's inventive contribution or the advantages obtained therewith.

An effort was made in the original rejection to identify those additional elements contained in the specific embodiments that were described in the instant specification with the belief that one or more of those elements provided the structural elements needed to reflect Applicant's inventive contribution in the pending claims. Applicant's response has convincingly shown that none of the elements identified therein are distinguishing. It is, therefore, Applicant's responsibility to identify that material element or combination of elements that was present in the cells that were described in the working example of the instant application that permitted "only proper combinations" of those portions of the claimed vectors to be produced and to incorporate that element or combination of elements into the claims. As stated in the original rejection, claims which omit elements which are critical or essential to the practice of the invention are not enabled by the disclosure and the instant claims do not recite sufficient material elements to provide the functionality required of a vector of the instant invention. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

Applicant has stated that the elements recited in claim 16, for example, "are sufficient to point out and that which Applicant regards as the invention". Applicant is advise that a claim must not only recited those elements which distinguishes the claimed invention from the art but must also recite sufficient elements to produce an invention which not only works but which also reflects Applicant's inventive contribution and the instant claims do not do this. In fact, there is not a single element in claim 1 which reflects Applicant's inventive contribution of providing a system of two vectors which only form proper combinations of first and second DNAs as expressly identified in the instant specification.

9) Claims 7, 8 and 77 are rejected under 35 U.S.C. § 112, first paragraph, because the instant specification does not provide the guidance needed to produce bacteriophage in a cell which is not bacterial.

10) Claims 1 to 5, 7, 8, 16 to 33 and 66 to 77 stand rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential elements as explained above, such omissions amounting to gaps between the elements. See MPEP § 2172.01.

11) Claims 7, 26 to 33 and 77 stand rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections for those reasons of record as applied to claims 6 to 8, 22 to 24 and 31 to 33 in section 12.1 of Paper Number 12. Claim 26 is now particularly confusing because it is unclear if each of the "plurality of expression vectors" is supposed to contain a "first and second DNA sequence" or if the first and second DNA sequences are to be encoded by separate vectors. See MPEP § 2172.01.

13) Claims 1 to 5 and 25 to 30 stand rejected under 35 U.S.C. § 103 as being unpatentable over the Huse et al. publication (Science 246:1275-1281, 1989) in view of the Ladner et al. publication (WO 88/06630, 1988). The subject of these claims differs from the cells, vectors, and cloning system disclosed in the Huse et al. reference in having the receptor protein of the instant invention expressed on the surface of a host cell as opposed to that disclosed in the Huse reference which is confined to the host cell cytoplasm. Applicant has traversed this rejection on the premise that, in the absence of the instant specification, an artisan would not have been motivated to express an antibody molecule such as those produced by Huse et al. on the surface of a host cell or viral

package. On the contrary, ample motivation for the expression of any binding protein on the surface of a cell of virus can be found in the first paragraph of the section entitled "DESCRIPTION OF PREFERRED EMBODIMENTS" on pages 2 and 3 of the Ladner et al. publication. This reference expressly taught that "[a]ny protein or antibody domain for which a gene can be isolated or constructed may be displayed in the outer surface of an organism into which the gene has been inserted" and that "[t]he organism so produced may be easily isolated from organisms which do not contain the desired gene".

Applicant's assertion that only the instant specification teaches that DNAs encoding two independent polypeptides can be combined and expressed at the cell surface is factually incorrect. The natural expression of heterodimeric and even heteropentameric receptor protein complexes was well known in the art prior to the time of the instant invention. Further, there is no actual evidence of record that both of the polypeptides expressed by the bacteriophage of the instant specification actually associate on the surface of those bacteriophage to form a "heteromeric receptor". The binding activity detected by Applicant can readily be attributable to a single V_H domain. However, because it was well known in the art prior to the making of the instant invention that antibody V_H and V_L domains spontaneously associate, it has been assumed that the co-expression of these two types of polypeptides in a single virus or organism in which one or both were fused to a cell surface protein would result in the production of a V_HV_L complex. It is a knowledge of the art prior to Applicant's invention, and not the instant specification, which supports both the instant rejection and the conclusion that the instant invention works as claimed. If Applicant essentially argues that the prior art was not enabled for the co-expression of a heterodimeric receptor of the surface of a cell or

virus then such arguments will be used as a basis for concluding that the claimed invention does work since there is no evidence of record that a V_HV_L complex has actually been produced on the surface of the bacteriophage described in the instant specification.

14) Claims 6 to 8, 22 to 24, and 31 to 33 stand rejected under 35 U.S.C. § 103 as being unpatentable over the Huse et al. and Ladner et al. references as applied to claims 1 to 5, 16 to 21, and 25 to 30 above, and further in view of the Parmley et al. publication (GENE 73:305-318, 1988) for those reasons of record.. These claims further limit those above to the use of a filamentous bacteriophage vector. The Parmley reference has been relied upon exclusively to show that the use of a filamentous bacteriophage vector to obtain the surface expression of a potential binding protein on the surface of a bacteriophage to facilitate the purification of only those bacteriophage containing a recombinant nucleic acid encoding proteins with a desired binding property was a practice that was known in the art prior to the making of the instant invention. Applicant has not identified the error inj this showing.

15) Claims 1 to 5 and 25 to 30 are rejected under 35 U.S.C. § 103 as being unpatentable over the Sastry et al. publication (P.N.A.S. 86:5728-5732, 1989) in view of the Ladner et al. (WO 88/06630, 1988) and Robinson et al. (WO 87/02671) publications for those reasons of record. Applicant has essentially traversed this rejection for those reasons as applied to the Huse et al. and Ladner et al. references above and those arguments were not found persuasive for those reasons given above.

16) Claims 6 to 8, 22 to 24, and 31 to 33 stand rejected under 35 U.S.C. § 103 as being unpatentable over the Sastry et al., Ladner et al., and Robinson et al. publications as applied to claims

1 to 5, 16 to 21, and 25 to 30 above, and further in view of the Parmley et al. reference (GENE 73:305-318, 1988) for those reasons of record.

17) Applicant's arguments filed 24 September of 1998 have been fully considered but they are not persuasive.

18) **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (703) 308-4008. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached at (703) 308-2731.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JOHN ULM
PRIMARY EXAMINER
GROUP 1800